CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074842

Trade Name : ETODOLAC CAPSULES

Generic Name: Etodolac Capsules 200mg and 300mg

Sponsor : Endo Laboratories, L.L.C.

Approval Date: July 17, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074842

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074842

APPROVAL LETTER

ANDA 74-842

JUL 17 1997

Endo Laboratories, L.L.C.
Attention: Andrew G. Clair, Ph.D.
1000 Stewart Avenue
Garden City, NY 11530

Dear Sir:

This is in reference to your abbreviated new drug application dated January 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etodolac Capsules, 200 mg and 300 mg.

Reference is also made to your amendments dated May 22; June 11, 24, 26, and 30; and July 8, and 9, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Etodolac Capsules, 200 mg and 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Lodine® Capsules 200 mg and 300 mg, respectively, of Wyeth Ayerst Laboratories, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

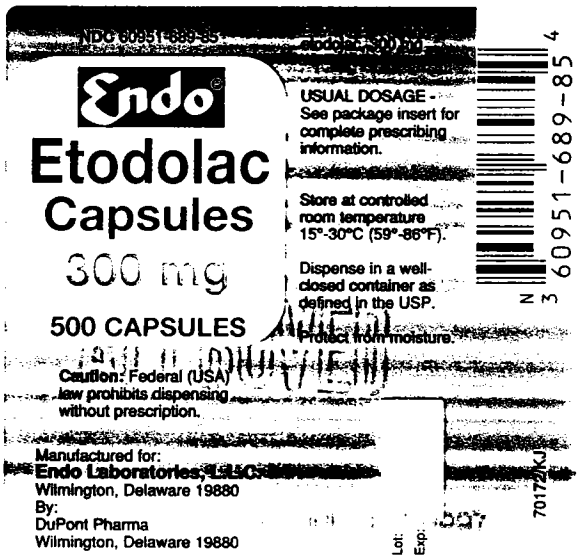
Sincerely yours,

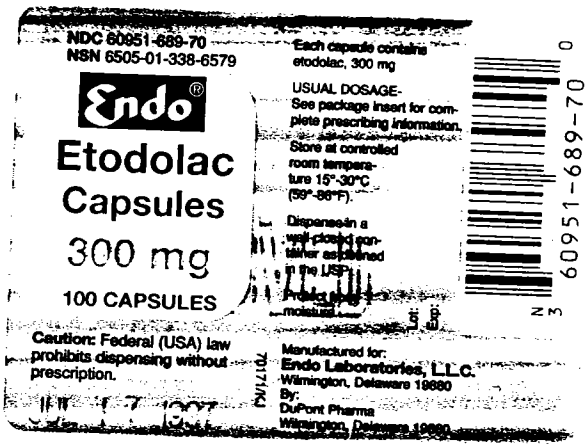
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

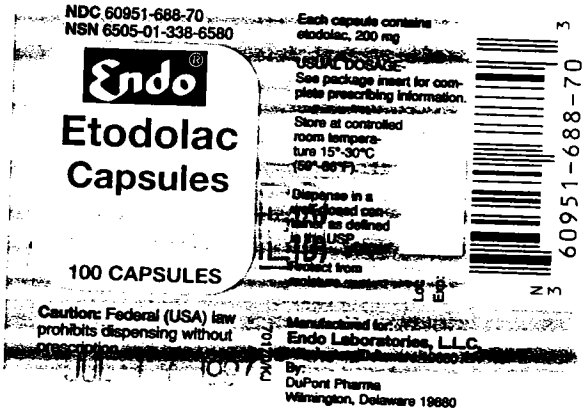
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074842

FINAL PRINTED LABELING

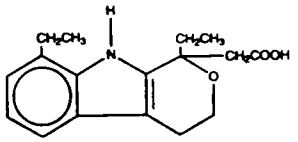

NDC 60951-689-85
Endo
Etodolac
Capsules
300 mg
500 CAPSULES
USUAL DOSAGE -
See package insert for complete prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a well-closed container as defined in the USP.
Protect from moisture.
Caution: Federal (USA) law prohibits dispensing without prescription.
Manufactured for:
Endo Laboratories, LLC
Wilmington, Delaware 19880
By:
DuPont Pharma
Wilmington, Delaware 19880
Lot:
Exp:
N 3 60951-689-85 4


NDC 60951-689-70
NSN 6505-01-338-6579
Endo®
Etodolac
Capsules
300 mg
100 CAPSULES
Caution: Federal (USA) law prohibits dispensing without prescription.
Each capsule contains etodolac, 300 mg
USUAL DOSAGE-
See package insert for complete prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a well-closed container as defined in the USP.
Protect from moisture.
Lot
Exp
Manufactured for:
Endo Laboratories, LLC.
Wilmington, Delaware 19880
By:
DuPont Pharma
Wilmington, Delaware 19880
0 60951-689-70 3


NDC 60951-688-70
NSN 6505-01-338-6580
Endo®
Etodolac
Capsules
100 CAPSULES
Each capsule contains etodolac, 200 mg
USUAL DOSAGE:
See package insert for complete prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a tight, closed container as defined in the USP
Protect from
Caution: Federal (USA) law prohibits dispensing without prescription.
Manufactured for:
Endo Laboratories, L.L.C.
By:
DuPont Pharma
Wilmington, Delaware 19880
60951-688-70

ETODOLAC CAPSULES

Description
Etodolac is a pyranocarboxylic acid chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The structural formula for etodolac is shown below:



The molecular formula for etodolac is $C_{17}H_{21}NO_3$. The molecular weight of the base is 287.37. It has a pKa of 4.65 and an n-octanol:water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

Each capsule, for oral administration, contains etodolac, 200 mg or 300 mg. In addition, each capsule contains the following inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate and sodium starch glycolate. The capsule shell contains gelatin, titanium dioxide, FD&C Yellow No. 6, red iron oxide and yellow iron oxide.

Clinical Pharmacology
PHARMACOLOGY
Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac, like that of other NSAIDs, is not known but is believed to be associated with the inhibition of prostaglandin biosynthesis.

Etodolac is a racemic mixture of [-]R- and [+]S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the [+]S-form is biologically active. Both enantiomers are stable and there is no [-]R to [+]S conversion *in vivo*.

PHARMACODYNAMICS
Analgesia was demonstrable 1/2 hour following single doses of 200 to 400 mg etodolac, with the peak effect occurring in 1 to 2 hours. The analgesic effect generally lasted for 4 to 6 hours (see **Clinical Trials**).

PHARMACOKINETICS
The pharmacokinetics of etodolac have been evaluated in 267 normal subjects, 44 elderly patients (>65 years old), 19 patients with renal failure (creatinine clearance 37 to 88 mL/min), 9 patients on hemodialysis, and 10 patients with compensated hepatic cirrhosis.

Etodolac, when administered orally, exhibits kinetics that are well described by a two-compartment model with first-order absorption.

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin, glyburide, furosemide or hydrochlorothiazide.

ABSORPTION
Etodolac is well absorbed and had a relative bioavailability of 100% when 200 mg capsules were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from either the tablet or capsule formulation, is at least 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. Mean (±1 SD) peak plasma concentrations range from approximately 14 ± 4 to 37 ± 9 µg/mL after 200 to 600 mg single doses and are reached in 80 ± 30 minutes (see Table 1 for summary of pharmacokinetic parameters). The dose-proportionality based on AUC (the area under the plasma concentration-time curve) is linear following doses up to 600 mg every 12 hours. Peak concentrations are dose-proportional for both total and free etodolac following doses up to 400 mg every 12 hours, but following a 600 mg dose, the peak is about 20% higher than predicted on the basis of lower doses.

Table 1. Etodolac Steady-State Pharmacokinetic Parameters
(N=267)

Kinetic Parameters	Mean ± SD
Extent of oral absorption (bioavailability) [F]	≥ 80%
Oral-dose clearance [CL/F]	47 ± 16 mL/h/kg
Steady-state volume [V_{ss}/F]	362 ± 129 mL/kg
Distribution half-life [$t_{1/2}$, α]	0.71 ± 0.50 h
Terminal half-life [$t_{1/2}$, β]	7.3 ± 4.0 h

Antacid Effects
The extent of absorption of etodolac is not affected when etodolac is administered with an antacid. Coadministration with an antacid decreases the peak concentration reached by about 15 to 20%, with no measurable effect on time-to-peak.

Food Effects
The extent of absorption of etodolac is not affected when etodolac is administered after a meal. Food intake, however, reduces the peak concentration reached by approximately one half and increases the time-to-peak concentration by 1.4 to 3.8 hours.

Distribution
Etodolac has an apparent steady-state volume of distribution about 0.362 L/kg. Within the therapeutic dose range, etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied.

Metabolism
Etodolac is extensively metabolized in the liver, with renal elimination of etodolac and its metabolites being the primary route of excretion. The intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

Protein Binding
Data from *in vitro* studies, using peak serum concentrations at reported therapeutic doses in humans, show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.

Elimination
The mean plasma clearance of etodolac, following oral dosing is 47 (± 16) mL/h/kg, and terminal disposition half-life is 7.3 (± 4.0) hours. Approximately 72% of the administered dose is recovered in the urine as the following, indicated as % of the administered dose:

–etodolac, unchanged	1%
–etodolac glucuronide	13%
–hydroxylated metabolites (6-, 7-, and 8-OH)	5%
–hydroxylated metabolite glucuronides	20%
–unidentified metabolites	33%

Fecal excretion accounted for 16% of the dose.

SPECIAL POPULATIONS
Elderly Patients
In clinical studies, etodolac clearance was reduced by about 15% in older patients (>65 years of age). In these studies, age was shown not to

Pre-existing Asthma
About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, etodolac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

INFORMATION FOR PATIENTS
Etodolac, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

Physicians may wish to discuss with their patients the potential risks (see **Warnings, Precautions, Adverse Reactions**) and likely benefits of nonsteroidal anti-inflammatory drug treatment.

Patients on etodolac should report to their physicans signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Because serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this follow-up (see **Warnings**–RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY THERAPY).

Patients should also be instructed to seek medical emergency help in case of an occurrence of anaphylactoid reactions (see **Warnings**).

LABORATORY TESTS
Patients on long-term treatment with etodolac, as with other NSAIDs, should have their hemoglobin or hematocrit checked periodically for signs or symptoms of anemia. Appropriate measures should be taken in case such signs of anemia occur.

If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g., eosinophilia, rash, etc.) and if abnormal liver tests are detected, persist or worsen, etodolac should be discontinued.

DRUG INTERACTIONS
Antacids
The concomitant administration of antacids has no apparent effect on the extent of absorption of etodolac. However, antacids can decrease the peak concentration reached by 15% to 20% but have no detectable effect on the time-to-peak.

Aspirin
When etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free etodolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.

Warfarin
Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and etodolac results in reduced protein binding of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and etodolac should not require dosage adjustment of either drug. However, there have been a few spontaneous reports of prolonged prothrombin times in etodolac-treated patients receiving concomitant warfarin therapy. Caution should be exercised because interactions have been seen with other NSAIDs.

Cyclosporine, Digoxin, Lithium, Methotrexate
Etodolac, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels of digoxin, lithium, and methotrexate and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs.

Phenylbutazone
Phenylbutazone causes increase (by about 80%) in the free fraction of etodolac. Although *in vivo* studies have not been done to see if etodolac clearance is changed by coadministration of phenylbutazone, it is not recommended that they be coadministered.

DRUG/LABORATORY TEST INTERACTIONS
The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose-relationship has been observed.

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dL were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m^2, respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3.0 to 5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 µg/mL) compared to negative controls (2.0%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m^2). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

PREGNANCY
Teratogenic Effects–Pregnancy Category C
In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2 to 14 mg/kg/day) close to human clinical doses. However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose-response relationship.

There are no adequate or well-controlled studies in pregnant women. Etodolac should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arteriosus, use during late pregnancy should be avoided.

LABOR AND DELIVERY
In rat studies with etodolac, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of etodolac on labor and delivery in pregnant women are unknown.

NURSING MOTHERS
It is not known whether etodolac is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etodolac, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established.

GERIATRIC POPULATION
As with any NSAID, however, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose because the elderly seem to tolerate NSAID side effects less well than younger patients. In patients 65 years and older, no substantial differences in the side effect profile of etodolac were seen compared with the general population (see **Clinical Pharmacology**–PHARMACOKINETICS).

Adverse Reactions
Adverse-reaction information for etodolac was derived from 2,629 arthritic patients treated with etodolac in double-blind and open-label clinical trials of 4 to 320 weeks in duration and worldwide postmarketing surveillance studies. In clinical trials, most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials, because of adverse events, was up to 10% for patients treated with etodolac.

New patient complaints (with an incidence greater than or equal to 1%) are listed below by body system. The incidences were determined from clinical trials involving 465 patients with osteoarthritis treated with 300 to 500 mg of etodolac b.i.d. (i.e., 600 to 1000 mg/day).

INCIDENCE GREATER THAN OR EQUAL TO 1%—PROBABLY CAUSALLY RELATED
Body as a whole—Chills and fever.
Digestive system—Dyspepsia (10%), abdominal pain*, diarrhea*, flatulence*, nausea*, constipation, gastritis, melena, vomiting.
Nervous system—Asthenia/malaise*, dizziness*, depression, nervousness.
Skin and appendages—Pruritus, rash.
Special senses—Blurred vision, tinnitus.
Urogenital system—Dysuria, urinary frequency.

*Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac.

Drug-related patient complaints occurring in fewer than 3%, but more than 1%, are unmarked.

INCIDENCE LESS THAN 1%—PROBABLY CAUSALLY RELATED (Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized)
Body as a whole—*Allergic reactions, anaphylactoid reaction.*
Cardiovascular system—Hypertension, congestive heart failure, flushing, palpitations, syncope, *vasculitis (including necrotizing and allergic).*
Digestive system—Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, *cholestatic hepatitis,* hepatitis, *cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis,* peptic ulcer with or without bleeding and/or perforation, *intestinal ulceration, pancreatitis.*
Hemic and lymphatic system—Ecchymosis, anemia, thrombocytopenia, bleeding time increased, *agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.*
Metabolic and nutritional—Edema, serum creatinine increase, *hyperglycemia in previously controlled diabetic patients.*
Nervous system—Insomnia, somnolence.
Respiratory system—Asthma.
Skin and appendages—Angioedema, sweating, urticaria, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome,* hyperpigmentation, *erythema multiforme.*
Special senses—Photophobia, transient visual disturbances.
Urogenital system—*Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.*

INCIDENCE LESS THAN 1%—CAUSAL RELATIONSHIP UNKNOWN (Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians)
Body as a whole—Infection, headache.
Cardiovascular system—Arrhythmias, myocardial infarction, cerebrovascular accident.
Digestive system—Esophagitis with or without stricture or cardiospasm, colitis.
Metabolic and nutritional—Change in weight.
Nervous system—Paresthesia, confusion.
Respiratory system—Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis.
Skin and appendages—Alopecia, maculopapular rash, photosensitivity, skin peeling.
Special senses—Conjunctivitis, deafness, taste perversion.
Urogenital system—Cystitis, hematuria, leukorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities.

Overdosage
Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur and coma has occurred following massive ibuprofen or mefenamic-acid overdose. Hypertension, acute renal failure, and respiratory depression may occur but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, alkalinization of the urine, hemodialysis, or hemoperfusion would probably not be useful due to etodolac's high protein binding.

Dosage and Administration
As with other NSAIDs, the lowest dose and longest dosing interval should be sought for each patient. Therefore, after observing the response to initial therapy with etodolac, the dose and frequency should be adjusted to suit an individual patient's needs.

Dosage adjustment of etodolac is generally not required in patients with mild to moderate renal impairment. Etodolac should be used with caution in such patients, because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function. (see **Precautions**–GENERAL PRECAUTIONS, *Renal Effects).*

ANALGESIA
The recommended total daily dose of etodolac for acute pain is up to 1000 mg, given as 200-400 mg every 6 to 8 hours. In some patients, if the potential benefits outweigh the risks; the dose may be increased to 1200 mg/day in order to achieve a therapeutic benefit that might not have been achieved with 1000 mg/day. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

OSTEOARTHRITIS
The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis is: 300 mg b.i.d., t.i.d., or 400 mg b.i.d., or 500 mg b.i.d. During long-term administration, the dose of etodolac may be adjusted up or down depending on the clinical response of the patient. A lower dose of 600 mg/day may suffice for long-term administration. In patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. When treating patients with higher doses, the physician should observe sufficient increased clinical benefit to justify the higher dose. Physicians should be aware that doses above 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

In chronic conditions, a therapeutic response to therapy with etodolac is sometimes seen within one week of therapy, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

How Supplied
Etodolac Capsules are supplied as follows:
200 mg - white to off-white granules in gelatin capsules with yellow opaque cap/ivory opaque body. Axial imprinted in red color "Endo 688" on both cap and body.

Bottles of 100

300 mg - white to off-white granules in gelatin capsules with yellow opaque cap/yellow opaque body. Axial imprinted in red color "Endo 689" on both cap and body.

Bottles of 100
Bottles of 500

Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a well-closed container as defined in the USP. Protect from moisture.
Caution: Federal (USA) law prohibits dispensing without prescription.

Manufactured By:
DuPont Pharma
Wilmington, Delaware 19880

6433-01/Rev. May, 1997

have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, on the basis of body size (see **Precautions**–GERIATRIC POPULATION), as they may be more sensitive to antiprostaglandin effects than younger patients (see **Precautions**–GERIATRIC POPULATION).

Renal Impairment
Studies in patients with mild-to-moderate renal impairment (creatinine clearance 37 to 88 mL/min) showed no significant differences in the disposition of total and free etodolac. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac, due to a 50% greater unbound fraction. Free etodolac clearance was not altered, indicating the importance of protein binding in etodolac's disposition. Nevertheless, etodolac is not dialyzable.

Hepatic Impairment
In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Although no dosage adjustment is generally required in this patient population, etodolac clearance is dependent on hepatic function and could be reduced in patients with severe hepatic failure.

Clinical Trials
ANALGESIA
Controlled clinical trials in analgesia were single-dose, randomized, double-blind, parallel studies in three pain models, including dental extractions. The analgesic effective dose for etodolac established in these acute pain models was 200 to 400 mg. The onset of analgesia occurred approximately 30 minutes after oral administration. Etodolac 200 mg provided efficacy comparable to that obtained with aspirin (650 mg). Etodolac 400 mg provided efficacy comparable to that obtained with acetaminophen with codeine (600 mg + 60 mg). The peak analgesic effect was between 1 to 2 hours. Duration of relief averaged 4 to 5 hours for 200 mg of etodolac and 5 to 6 hours for 400 mg of etodolac as measured by when approximately half of the patients required remedication.

OSTEOARTHRITIS
The use of etodolac in managing the signs and symptoms of osteoarthritis of the hip or knee was assessed in double-blind, randomized, controlled clinical trials in 341 patients. In patients with osteoarthritis of the knee, etodolac, in doses of 600 to 1000 mg/day, was better than placebo in two studies. The clinical trials in osteoarthritis used b.i.d. dosage regimens.

Indications and Usage
Etodolac is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis. Etodolac is also indicated for the management of pain.

Contraindications
Etodolac is contraindicated in patients with known hypersensitivity to etodolac. Etodolac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to etodolac have been reported in such patients (see **Warnings**–ANAPHYLACTOID REACTIONS).

Warnings
RISK OF GASTROINTESTINAL (GI) ULCERATION, BLEEDING, AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) THERAPY
Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of such agents for several months' to 2 years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appears to occur in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

ANAPHYLACTOID REACTIONS
Anaphylactoid reactions may occur in patients without prior exposure to etodolac. Etodolac should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other nonsteroidal anti-inflammatory drugs. Fatal reactions have been reported in such patients (see **Contraindications** and **Precautions**–*Pre-existing Asthma).* Emergency help should be sought in cases where an anaphylactoid reaction occurs.

ADVANCED RENAL DISEASE
In cases with advanced kidney disease, as with other NSAIDs, treatment with etodolac should only be initiated with close monitoring of the patient's kidney function (see **Precautions**–*Renal Effects).*

PREGNANCY
In late pregnancy, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus (see **Precautions**–*Teratogenic Effects–Pregnancy Category C).*

Precautions
GENERAL PRECAUTIONS
Renal Effects
As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study.

A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction; those taking diuretics; and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in **Adverse Reactions**) may be attributable to these metabolites should be considered.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including etodolac. These abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Meaningful elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with etodolac. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with etodolac. Rare cases of liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), etodolac should be discontinued.

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs including etodolac. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including etodolac, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

Fluid Retention and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs, including etodolac. Therefore, etodolac should be used with caution in patients with fluid retention, hypertension, or heart failure.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074842

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 3

2. ANDA 74-842

3. NAME AND ADDRESS OF APPLICANT
Endo Laboratories, L.L.C.
Attention: Andrew G. Clair
1000 Stewart Avenue
Garden City, NY 11530

4. LEGAL BASIS FOR SUBMISSION see next page

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Etodolac Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES: see next page

10. PHARMACOLOGICAL CATEGORY
NSAID

11. Rx or OTC
Rx

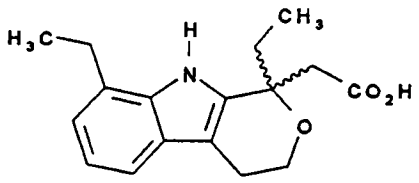
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsules

14. POTENCY
200 & 300 mg

15. CHEMICAL NAME AND STRUCTURE

(±)-1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid



$C_{17}H_{21}NO_3$ [*41340-25-4*]

M.W. = 287.36

16. RECORDS AND REPORTS N/A

17. COMMENTS see next page

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: APPROVAL.

19. REVIEWER: J. L. Smith DATE COMPLETED: June 6, 1997 & July 1, 1997

cc: ANDA 74-842
Division File

Endorsements:
HFD-623/J.Smith/7-1-97
HFD-623/V.Sayeed/7-9-97
X:\NEW\FIRMSAM\ENDO\LTRS&REV\74842AP3.CD
F/T by: bc/7-10-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074842

BIOEQUIVALENCE REVIEW(S)

D\V

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #74-842 SPONSOR: Endo Laboratories, L.L.C.
DRUG: Etodolac
DOSAGE FORM: Capsule
STRENGTHS: 200 mg and 300 mg
TYPE OF STUDY: Single dose, Fasting and Food
STUDY SITE:

STUDY SUMMARY: Fasting Study: Twenty-three subjects entered the study. Twenty-two subjects completed the study. AUC_{0-t} and AUC_{0-inf} of the test product were both 1% higher than the respective means of the reference product. The C_{max} of the test product was 8% lower than that for the reference product and occurred about 6 minutes earlier. The 90% confidence intervals for $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and C_{max} were 97.1-106%, 96.8-105%, and 81.8-103% respectively.
Food Study: All eighteen enrolled subjects completed the study. The test/reference ratios for mean AUC_{0-t}, AUC_{0-inf}, and C_{max} were 1.05, 1.04, and 1.09 respectively. The mean C_{max} for the test product was 9% higher than that of reference product and occurred about 10 minutes later. Fasting and food studies are acceptable.

DISSOLUTION: The dissolution testing was done by the method which is same as recommended by the agency. The formulation for 200 mg capsule is proportionally similar to 300 mg capsule. Both strengths of the capsules dissolve greater than in 20 minutes. The dissolution results are acceptable. The waiver of *in vivo* bio-study for 200 mg strength of the product is granted.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: _____ DATE 6/10/96

BRANCH CHIEF: Shriniwas Nerurkar, Ph.D., BRANCH: II

INITIAL: _____ DATE 6/10/1996

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Keith Chan, Ph.D

INITIAL: _____ DATE 6/10/96

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

ANDA 74-842

Endo Laboratories, L.L.C.
Attention: Andrew G. Clair, Ph.D.
1000 Stewart Avenue
Garden City NY 11530

JUN 10 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Etodolac Capsules 200 mg and 300 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.5 at 37°C using apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

   Not less thar of the labeled amount of etodolac in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 6 1996

Etodolac
200 mg and 300 mg Capsules
ANDA #74-842
Reviewer: Kuldeep R. Dhariwal
File name: 74842SDW.196

Endo Laboratories, L.L.C.
1000 Stewart Avenue
Garden City, NY 11530
Submission Date:
January 31, 1996

Review of Fasting and Food Studies, Dissolution Data, and Waiver Request

The firm has submitted single-dose *in vivo* bioequivalence studies under fasting and fed conditions and dissolution data comparing its etodolac capsules, 300 mg with Wyeth-Ayerst's Lodine® capsules, 300 mg. The firm has also requested waiver of *in vivo* bioequivalence study requirements for its 200 mg capsules. To support the request, the firm has submitted comparative dissolution profiles on 200 mg of its product and reference listed drug Lodine®.

Introduction:

Etodolac is a pyranocarboxylic acid chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. Etodolac is a nonsteroidal antiinflammatory drug with antiinflammatory, analgesic, and antipyretic properties. The drug is a racemic mixture of R- and S-etodolac, the S-form being biologically active. Both enantiomers are stable and there is no R-to-S conversion *in vivo*. Etodolac is well absorbed with a relative bioavailability of 100% when 200 mg capsules were compared with a solution. The systemic availability is at least 80% and etodolac does not undergo significant first-pass metabolism following oral administration. When administered orally, etodolac exhibits characteristics which are well described by a two-compartment model with first-order absorption. Mean (± 1 SD) peak plasma concentrations range from approximately 14±4 to 37±9 μg/mL after 200 to 600 mg single doses and are reached in 80±30 minutes. The mean plasma clearance of etodolac is 47 (±16) mL/h/kg, and terminal disposition half-life is 7.3 (±4.0) hours. Intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

The extent of absorption of etodolac is not affected when etodolac is administered after a meal, but the C_{max} is reduced by 50% and T_{max} increased by 1.4-3.8 hours.

Etodolac is currently marketed as Lodine® manufactured by Wyeth-Ayerst and is available as 200 and 300 mg capsules and 400 mg tablets. Lodine® is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis, and also for the management of pain. The recommended dose for acute pain is 200-400 mg every 6-8 hours as needed, not to exceed a total daily dose of 20 mg/kg body weight. The recommended dose for osteoarthritis is initially 800 to 1200 mg/day in divided doses, followed by dosage adjustment within the range of 600 to 1200 mg/day given in divided doses. The total daily dose of Lodine® should not exceed 1200 mg. For patients weighing 60 kg or less, the total daily dose should not exceed 20 mg/kg.

Bioavailability of Etodolac Capsules, 300 mg under Fasting Conditions:

A. Objective: The objective of this study is to compare *in vivo* the rate and extent of oral absorption of etodolac capsules (300 mg) manufactured by The DuPont Merck Pharmaceutical Company for Endo Laboratories, L.L.C. with the rate and extent of oral absorption of Lodine® capsules (300 mg) manufactured by Wyeth-Ayerst Laboratories.

B. Study Sites and Investigators:

Clinical Site:

Analytical Site:

Clinical Investigator:
Medical Investigator:
Analytical Investigator:
Protocol #P95-276 "A single-dose crossover study in healthy male volunteers to determine the *in vivo* bioequivalence of etodolac 300 mg test and reference capsules" was approved by the Institutional Review Board.
Consent Form: A copy of the volunteer informed consent form used in the study is given on page 10 45 vol. 1.3.
Study Dates: Period I August 19-20, 1995
Period II August 26-27, 1995
Analysis Dates: October 9-23, 1995

C. Study Design:

The study was designed as a two-way, single-dose, open-label, two-period, two-treatment crossover study with a one week wash-out period between drug administrations. The subjects were housed in a dormitory facility from approximately 10 hours prior to dosing until 36 hours after dosing. The subjects were assigned as follows:

Sequence	Subject number	Phase I	Phase II
1	1,2,3,4,5,7,9,12,16,17,19	A	B
2	6,8,11,13,14,15,18,20,21,22,23,24	B	A

A = Etodolac Capsules, 300 mg; Manufactured by DuPont Merck for Endo Laboratories; Lot #JH234B, Batch size: Theoretical Yield: capsules, Actual Yield: Manufacture Date: 8/95; Assay: 101%, Content Uniformity: 99.6%

B = Lodine® Capsules, 300 mg; Lot #3950231; Expiry Date: 1/98; Assay: 98.85%

The subjects fasted for 10 hours prior to dosing and until 4 hours postdose. Fluids were not allowed for 1 hour before and 2 hours after dosing. The drug products were administered with 240 mL of water. The subjects were not allowed to lie down or sleep for the first four hours after drug administration. Sitting blood pressure and heart rate were measured prior to dosing and at 4 and 24 hours postdose.

D. Subject Selection:

Twenty-three healthy male volunteers entered the study. Following inclusion criteria were used in selecting the subjects:

- 18-50 years of age, weight range within ±15% for height and body frame as per Desirable Weights for Men - 1983 Metropolitan Height and Weight Table
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits

Subjects were excluded from this study based on the following criteria:

- history of hypersensitivity to etodolac or other NSAID drugs
- presence of any disease or condition which might compromise the hematopoietic, renal, hepatic, endocrine, pulmonary, central nervous, cardiac, or gastrointestinal systems
- history of aspirin induced asthma or urticaria, nasal polyps, serious mental disorders
- blood pressure of 100/60 mm Hg or lower at screening or check-in
- use of recreational drugs or history of drug addiction
- history of alcohol or drug abuse
- blood/plasma donation within 30 days prior to the study
- positive HIV, hepatitis B surface antigen
- participation in a clinical study within 30 days prior to the study (60 days for investigational drugs with an elimination half-life greater than 10 days)

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days or OTC medications within 7 days of the first drug administration
- no caffeine containing foods or beverages within 48 hours
- no strenuous physical activity during the in-house portion of the study

E. Sample Collection:

Ten milliliters of venous blood were obtained in heparinized Vacutainers at 0 (predose), 0.25, 0.50, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hours postdose. The samples remained at the collection station until all samples had been collected for that collection period. The samples were then transferred to the processing lab and centrifuged at 2400 rpm for 15 minutes at 4°C. The plasma was separated and stored at -20°C. The samples were shipped to the analytical facility on dry ice.

F. Analytical Methods:

G. Pharmacokinetics/Statistical Analysis:

Area under the concentration-time curve (AUC) was calculated by trapezoidal rule between consecutive blood drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration [C(T)]. AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C(T)/KE. The elimination rate constant (KE) was estimated by linear least squares fitting of the logarithm of the concentrations over the terminal phase of elimination versus time. Half-life, C_{max}, T_{max} were also calculated. The statistical analyses were performed using SAS software. The ratio of the mean test value to mean reference value and for the power of the ANOVA to detect a 20%

difference from the reference mean were performed using the LSMEAN values and standard error of estimate values. The ratios of geometric means and the 90% confidence intervals of the log (base e) transformed data were calculated.

H. Results:

1. Clinical:

Twenty-three subjects entered the study. Subject #17 dropped out for period II. Twenty-two subjects completed the study. Clinical vital signs were measured before dosing and at 4 and 24 hours after dosing. Each subject completed the study exit procedures within 14 days after the last blood sample collection. The exit procedures included general observations, physical examination, blood chemistry, hematology, and urine analysis.

Adverse events:

Following four subjects experienced headaches during the study, which were mild in nature.

Subject #	Period	Product	Sign/Symptom
4	I	*	Headache
7	I	*	Headache
15	I	Ref	Headache
19	**		Headache
19	II	Ref	Headache

* Headache started before dosing
** Headache started 4 days after period I dosing (test drug)

Subject #22 had elevated blood glucose at the end of the study and require follow-up tests and evaluation.

Deviations in the study:

1. Subject #7 donated plasma 15 days before start of the study.
2. Following deviations in scheduled phlebotomy times were reported:

Subject #	Period	Sampling time	Deviation
9	I	0:15	3 minutes late
15		0:15	3 minutes late
2		0:45	1 minute late
15		0:45	1 minute late
15		1:00	2 minutes late
8		1:20	1 minute late

8		3:00	1 minute late
4		4:00	4 minutes late
8	II	0:45	1 minute late
9		2:00	1 minute late

Actual blood draw times were used for calculations.

Reassays:

Following three samples were reassayed for the reasons shown against them:

# of samples	Reason for reassay
1	low injection
2	anomalous value

2. Analytical: Samples from both periods for a given subject were

3. Pharmacokinetics/Statistics:

The mean plasma concentrations of etodolac at each time point after test and reference products are shown in Table 1. There was no significant difference in mean plasma concentrations at any time point except at 0.25 hours. The time courses of etodolac concentrations after the two products are plotted in Figures 1 and 2. The pharmacokinetic parameters are summarized in Table 2. There were no significant differences between the formulations for any parameter. Based on the least squares means, the AUC_{0-t} and AUC_{0-inf} of the test product were both 1% higher than the respective means of the reference product. The C_{max} of the test product was 8% lower than that for the reference product and occurred about 6 minutes earlier. The reviewer performed some calculations to determine the accuracy of the values given in the application:

Drug Product: Etodolac (Test)

Subject #	Reviewer		Firm	
	AUC_{0-t}	AUC_{0-inf}	AUC_{0-t}	AUC_{0-inf}
4	144.56	148.70	144.90	149.05
11	137.20	141.56	137.21	141.57
24	104.69	109.02	104.33	108.67

The results of these calculations indicate good agreement between reviewer's calculations and the data reported by the firm.

The individual mean ratio for AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 3. The test/reference ratio for AUC_{0-t} ranged from (mean 1.02), AUC_{0-inf} ranged from (mean 1.01), and for C_{max} ranged from with a mean of 0.97.

Table 4 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios range from for test and for reference product.

Following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
$LNAUC_{0-t}$	97.1-106%	97.14-105.91%
$LNAUC_{0-inf}$	96.8-105%	96.79-105.48%
LNC_{max}	81.8-103%	81.83-103.37%

The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125%. Statistical analysis of data did not show any significant period or treatment effect. However, there was significant sequence effect for C_{max} (p=0.0755) and LNC_{max} (p=0.0825).

Bioavailability of Etodolac capsules, 300 mg: Food Study

A. Objective: (1) To compare the etodolac plasma levels produced after administration of the test formulation, with those produced after administration of a marketed reference product, when both products are administered after a standard meal
(2) To compare the etodolac plasma levels produced after administration of the test formulation, following a standard meal with those produced after administration of the same test formulation, after an overnight fast

B. Study Sites and Investigators:

Clinical Site:

Analytical Site:

Clinical Investigator:
Medical Investigator:
Analytical Investigator:
Protocol #P95-277 "A single-dose three-way crossover study in healthy volunteers to determine the effects of food on the bioavailability of etodolac 300 mg test and reference capsules" was approved by the Institutional Review Board.
Consent Form: A copy of the volunteer informed consent form used in the study is given on page 10 50 vol. 1.6.
Study Dates: Period I August 26-27, 1995
Period II September 02-03, 1995
Period III September 09-10, 1995
Analysis Dates: 9/26/95 to 10/17/1995

C. Study Design:

The protocol was designed as a randomized, single oral dose, three-treatment, three-period, six-sequence crossover bioavailability study with a one week wash-out between drug administrations. The subjects were housed in a dormitory facility from approximately 10 hours prior to drug administration until 36 hours after drug administration. The subjects were assigned as follows:

Subject number	Period I	Period II	Period III
9,10,14	C	A	B
3,8,11	B	A	C
4,6,15	B	C	A
2,12,16	A	B	C
1,7,17	A	C	B
7,15,18	C	B	A

A = Etodolac Capsules, 300 mg following an over night fast; Manufactured by DuPont Merck for Endo Laboratories; Lot #JH234B
B = Etodolac Capsules, 300 mg following a standard breakfast; Manufactured by DuPont Merck for Endo Laboratories; Lot #JH234B
C = Etodolac Capsules, 300 mg following a standard breakfast; Wyeth-Ayerst; Lot #3950231

Lot numbers of drug products administered in this study were the same as those used for the fasting study.

D. Subject Selection:

Eighteen healthy non-smoking male subjects were enrolled in the study with essentially same inclusion and exclusion criteria as in the fasting study. They were subjected to same screening procedure and restrictions.

E. Study Procedure:

Treatments B and C: Subjects were given a standard breakfast after a fast lasting at least 10 hours. The breakfast was served 30 minutes prior to dosing. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, six fluid oz. of orange juice and eight fluid oz. of whole milk. The drug was administered with 240 mL of water.

Treatment A: Subjects were given the assigned formulation with 240 mL of water after a fast of at least 10 hours.

F. Sample Collection, Analytical Methods, and Pharmacokinetics/Statistical Analysis:

Ten milliliters of venous blood were obtained in heparinized Vacutainers at 0 (predose), 0.25, 0.50, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hours postdose. The samples remained at the collection station until all samples had been collected for that collection period. The samples were then transferred to the processing lab and centrifuged at 2400 rpm for 15 minutes at 4°C. The plasma was separated and stored at -20°C. The samples were shipped to the analytical facility on dry ice.

Analytical methods, acceptance criteria, and statistical analysis were the same as for fasting study.

G. Results:

1. Clinical:

Eighteen subjects were enrolled in the study. All eighteen subjects completed the study. Vital signs were measured at 0 (predose), and at 4 and 24 hours post-dose.

Adverse events:

Five subjects reported adverse events:

Subj. #	Period	Product	Sign/Symptom
3	III	Ref-fed	Bee sting (left leg)
6	I	Test-fed	Headache
13	I	Ref-fed	Nausea
16	II	Test-fed	Headache
17	I	Test-fast	Dizziness, sweaty, pale, headache

All events were mild in nature.

Deviations in the study:

1. Subject #12 self-administered 500 mg Tylenol 4 days before period I dosing. Subject #13 took vitamin C 500 mg and one tablet of B-complex 4 days before period I dosing.
2. Following deviations in scheduled phlebotomy times were reported:

Subj. #	Period	Product	Time point	Deviation
6	I	Test-fed	0:15	1 minute late
17	I	Test-fast	0:45	1 minute late

7	I	Test-fast	1:00	1 minute late
17	I	Test-fast	1:00	2 minutes late
17	I	Test-fast	1:40	2 minutes late
17	I	Test-fast	2:00	No sample
4	I	Test-fed	3:00	2 minutes late
17	I	Test-fast	3:00	2 minutes late
7	I	Test-fast	4:00	1 minute late
17	I	Test-fast	24:00	2 minutes late
17	II	Ref-fed	0:15	1 minute late
18	II	Test-fed	1:00	2 minutes late
2	II	Test-fed	1:40	2 minutes late
1	III	Test-fed	0:30	1 minute late

Actual blood collection times were used in calculations.

2. Analytical:

3. Pharmacokinetics/Statistics:

The concentration of etodolac measured at each time point after each product is summarized in Table 5. These data indicate that with the exception of 0.25 to 1.33 hour and 3 hour samples, etodolac plasma concentrations in test fed were within 20% of that of the reference fed. The pharmacokinetic parameters are summarized in Table 6. The time courses of etodolac concentration after the three treatments are plotted in Figures 3 and 4.

When the test and reference formulations were administered after a meal, the least squares means for AUC_{0-t} and AUC_{0-inf} for the test formulation were 4 and 5% higher than the respective means for the reference formulation. The mean C_{max} for the test product was 9% higher than that of reference product and occurred about 10 minutes later.

The least squares means of AUC_{0-t} and AUC_{0-inf} were about 10% lower in test fed compared to test fasting conditions. The mean C_{max} was about 38% lower and 2 hours 16 minutes later in test fed compared to test fasting conditions.

Following are the ratios of the means of the pharmacokinetic parameters:

	Ratio of means (test/reference)
Test (Fed) vs. Reference (Fed)	
AUC_{0-t}	1.05
AUC_{0-inf}	1.04
C_{max}	1.09
Test (Fed) vs. Test (Fast)	
AUC_{0-t}	0.90
AUC_{0-inf}	0.91
C_{max}	0.62

Ratio of means between test and reference fed are within the acceptable limits of 0.80-1.20. The firm has provided following 90% confidence interval values for test (fed) vs. reference (fed):

AUC_{0-t}	100-108%
AUC_{0-inf}	99.6-108%
C_{max}	97.1-125%

Although not required for the food study, the 90% confidence intervals for these parameters are within the acceptable range of 80-125%.

In Vitro Dissolution Testing:

The dissolution testing was done using apparatus 1 (basket) at 100 rpm and 1000 mL of 0.05M phosphate buffer pH 7.5 as medium. The drug products used in the dissolution tests were from the same lots used in the *in vivo* bioequivalence studies. The firm is proposing a specification of not less than in 30 minutes. The test and reference products pass the dissolution tests using this criteria (Table 8).

Waiver Request:

The firm is requesting for a waiver of *in vivo* bioequivalence study for its 200 mg etodolac capsules. The comparative quantitative composition of 200 mg and 300 mg capsules is shown in Table 7. The firm has submitted the dissolution profile of its 200 mg capsule and compared it with the reference listed drug Lodine® 200 mg capsule.

Comments:

Fasting Study:

1. Twenty-three subjects entered the study. Subject #17 dropped out for period II. Twenty-two subjects completed the study. Four subjects experienced mild headaches during the study.

2. Based on the least squares means, the AUC_{0-t} and AUC_{0-inf} of the test product were both 1% higher than the respective means of the reference product. The C_{max} of the test product was 8% lower than that for the reference product and occurred about 6 minutes earlier.

3. The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125%. Statistical analysis of data did not show any significant period or treatment effect. However, there was significant sequence effect for C_{max} (p=0.0755) and LNC_{max} (p=0.0825). The study is acceptable as it meets the requirements given in division's guidance: statistical procedures for bioequivalence studies using a standard two-treatment crossover design, for studies showing a statistically significant sequence effect.

4. The study demonstrates that test product is bioequivalent to reference product.

Food Study:

1. Eighteen subjects were enrolled in the study. All eighteen subjects completed the study. Five subjects reported adverse events. All were mild in nature.

2. When the test and reference formulations were administered after a meal, the least squares means for AUC_{0-t} and AUC_{0-inf} for the test formulation were 4 and 5% higher than the respective means for the reference formulation. The mean C_{max} for the test product was 9% higher than that of reference product and occurred about 10 minutes later.

3. The least squares means of AUC_{0-t} and AUC_{0-inf} were about 10% lower in test fed compared to test fasting conditions. The mean C_{max} was about 38% lower and 2 hours 16 minutes later in test fed compared to test fasting conditions.

4. Ratio of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test fed and reference fed are within acceptable limits of 0.80-1.20.

5. The food study is acceptable.

Dissolution Testing:

There is no USP method available for dissolution testing of etodolac capsules. The firm has used the method which is same as recommended by the agency. The dissolution of 300 mg capsule is much slower at 5 and 10 minutes compared to reference 300 mg capsule. The test 300 mg capsule dissolves slower compared to test 200 mg capsule though both strengths are proportionally similar in excipients. Both strengths of test and reference capsules dissolve more than in 30 minutes. The dissolution data are acceptable. However, the firm would be recommended the specification of NLT (Q) in 20 minutes.

Not to be released under FOI: The other generic etodolac capsules were given specification of NLT (Q) in 20 minutes

Waiver Request:

1. The 200 mg and 300 mg capsules are proportionally formulated except for the filler. All excipients except filler in both strengths are present in the same amount in terms of % of active ingredient.

2. The dissolution profiles of test and reference capsules are similar except 5 and 10 minute time points. The reference product dissolved slower at early time points. Both the products dissolve greater than in 20 minutes. The waiver can be granted.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Endo Laboratories, on its etodolac capsules, 300 mg, lot #JH234, comparing it to the reference product Lodine® capsules, 300 mg, lot #3950231 manufactured by Wyeth-Ayerst has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Endo's etodolac capsule, 300 mg is bioequivalent to the reference product Lodine® capsule, 300 mg manufactured by Wyeth-Ayerst.

2. The *in vivo* bioequivalence study conducted under fed conditions by Endo Laboratories on its etodolac capsules, 300 mg, lot #JH234, comparing it to the reference product Lodine® capsules, 300 mg, lot #3950231 manufactured by Wyeth-Ayerst has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fed conditions, the bioavailability of Endo's etodolac capsule, 300 mg is similar to that of the reference product Lodine® capsule, 300 mg manufactured by Wyeth-Ayerst.

3. The dissolution testing conducted by Endo Laboratories on its etodolac 200 mg and 300 mg capsules is acceptable. The firm has conducted an acceptable *in vivo* bioequivalence study comparing its 300 mg capsules with 300 mg capsules of the reference product Lodine® manufactured by Wyeth-Ayerst. The formulation for 200 mg strength of the test product is proportionally similar to the 300 mg strength of the test product which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 200 mg capsules of the test product is granted. The 200 mg capsule of the test product is therefore deemed bioequivalent to the 200 mg capsule of Lodine® manufactured by Wyeth-Ayerst.

4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.5 at 37°C using apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

> Not less than of the labeled amount of etodolac in the dosage form is dissolved in 20 minutes.

5. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

The firm should be informed of the above recommendations.

Table 1

Etodolac Plasma Concentrations (μg/mL) in Fasting Study: Arithmetic Means ± Standard Deviation (N=22)

Time (h)	Test	Reference	Test/Ref
0	0	0	
0.25	0.621±0.609	1.695±0.984	0.37
0.50	7.877±5.935	10.816±6.766	0.73
0.75	14.098±7.68	13.715±8.773	1.03
1.00	14.322±6.67	14.296±8.347	1.00
1.33	14.267±6.41	15.360±6.714	0.93
1.67	14.563±6.12	14.656±6.399	0.99
2.00	14.552±4.67	14.371±4.881	1.01
2.50	14.263±3.86	13.079±3.596	1.09
3.00	12.860±3.15	11.991±3.007	1.07
4.00	10.549±2.57	10.930±3.719	0.96
6.00	4.981±1.223	4.687±1.187	1.06
8.00	3.435±1.003	3.240±0.853	1.06
10.0	2.628±0.845	2.553±0.761	1.03
12.0	2.380±0.810	2.222±0.670	1.07
16.0	1.466±0.556	1.448±0.589	1.01
24.0	0.647±0.378	0.634±0.382	1.02
36.0	0.124±0.240	0.118±0.219	1.05
Parameter			
AUC_{0-t} (μg/mLxh)	101.06±22.47	99.61±21.97	1.01
AUC_{0-inf} (μg/mLxh)	106.15±23.59	104.98±22.65	1.01
C_{max} (μg/mL)	20.305±4.915	21.964±5.60	0.92
T_{max} (h)	1.716±0.840	1.890±1.097	0.91
Half-life (h)	6.679±1.393	6.849±1.273	0.97
Rate constant	0.108±0.022 (h^{-1})	0.104±0.019	1.04

Table 2

Etodolac Plasma Concentrations in the Fasting Study (N=22)
Pharmacokinetic Parameters: Least Squares Means ± Standard Error

Parameter	Test	Reference	Test/Ref	90% confidence interval
AUC_{0-t} (μg/mLxh)	101.53±1.91	99.99±1.91	1.02	96.9-106%
AUC_{0-inf} (μg/mLxh)	106.66±1.98	105.35±1.98	1.01	96.6-106%
C_{max} (μg/mL)	20.398±0.95	22.162±0.95	0.92	81.6-103%
T_{max} (h)	1.731±0.19	1.832±0.19	0.94	69.0-120%
Half-life (h)	6.693±0.094	6.849±0.094	0.98	94.4-101%
Rate constant (h^{-1})	0.107±0.001	0.104±0.001	1.03	98.9-107%
$LNAUC_{0-t}$	4.598±0.017	4.583±0.017	1.00	97.1-106%
$LNAUC_{0-inf}$	4.647±0.017	4.637±0.017	1.00	96.8-105%
LNC_{max}	2.9845±0.047	3.0682±0.047	0.97	81.8-103%

Table 3

Test/Reference Ratio for Pharmacokinetic Parameters in the Fasting Study for Individual Subjects

Subject	Sequence	Ratio		
		AUC_{0-t}	AUC_{0-inf}	C_{max}
1	1	1.04	1.04	1.05
2	1	1.09	1.08	0.98
3	1	0.96	0.98	1.10
4	1	1.19	1.20	1.07
5	1	0.89	0.89	0.90
6	2	0.88	0.87	0.65
7	1	0.99	1.00	1.01
8	2	1.00	1.00	0.91
9	1	1.02	1.04	0.69
11	2	1.33	1.32	1.51
12	1	0.94	0.94	0.88
13	2	0.83	0.82	1.52
14	2	0.87	0.87	1.23
15	2	1.14	1.12	1.52
16	1	0.98	0.96	0.69
18	2	0.95	0.94	0.79
19	1	1.16	1.18	0.66
20	2	1.07	1.01	1.26
21	2	1.11	1.07	0.87
22	2	1.09	1.09	0.89
23	2	0.93	0.95	0.49
24	2	0.96	0.95	0.60

Table 4

AUC_{0-t}/AUC_{0-inf} Ratio for Individual Subjects in Fasting Study

Subject	AUC_{0-t}/AUC_{0-inf} Ratio	
	Test	Reference
1	0.96	0.96
2	0.95	0.95
3	0.91	0.93
4	0.97	0.97
5	0.97	0.97
6	0.97	0.97
7	0.94	0.94
8	0.97	0.97
9	0.96	0.97
11	0.97	0.97
12	0.96	0.95
13	0.96	0.94
14	0.95	0.94
15	0.94	0.92
16	0.95	0.93
18	0.93	0.92
19	0.94	0.95
20	0.95	0.90
21	0.95	0.91
22	0.97	0.97
23	0.93	0.95
24	0.96	0.96

Table 5

Etodolac Plasma Concentrations (μg/mL) in the Food Study (N=18)
Arithmetic Means ± Standard Deviation

Time h	Test-Fast A	Test-Fed B	Ref-Fed C	B/C	B/A	C/A
0	0.0	0.0	0.0			
0.25	0.281±0.54	0.00±0.0	0.039±0.17	0.0	0.0	0.14
0.50	8.881±8.38	0.111±0.21	0.388±0.81	0.29	0.01	0.04
0.75	13.59±8.86	0.273±0.49	0.783±1.18	0.35	0.02	0.06
1.00	14.57±7.21	0.632±0.88	1.696±2.66	0.37	0.04	0.12
1.33	14.52±5.19	1.469±1.81	2.633±2.84	0.56	0.10	0.18
1.67	16.47±5.56	3.561±4.16	3.998±2.99	0.89	0.22	0.24
2.00	15.27±4.13	5.503±4.53	5.592±3.89	0.98	0.36	0.37
2.50	13.59±3.98	8.549±4.89	7.545±3.67	1.13	0.63	0.55
3.00	11.75±3.28	11.73±4.50	9.133±3.37	1.28	0.99	0.78
4.00	10.02±3.65	11.45±3.89	11.88±3.81	0.96	1.14	1.19
6.00	4.812±1.34	7.762±2.37	7.062±2.03	1.10	1.61	1.47
8.00	3.277±0.99	4.146±1.34	3.824±1.10	1.08	1.26	1.17
10.0	2.506±0.69	3.121±1.15	2.885±0.89	1.08	1.24	1.15
12.0	2.236±0.54	2.777±0.96	2.536±0.74	1.09	1.24	1.13
16.0	1.256±0.50	1.470±0.65	1.402±0.56	1.05	1.17	1.12
24.0	0.575±0.31	0.687±0.49	0.743±0.48	0.92	1.19	1.29
36.0	0.075±0.18	0.116±0.25	0.115±0.24	1.01	1.55	1.53
Parameters						
AUC_{0-t} (μg/mLxh)	96.08±19.17	86.64±19.68	82.85±17.05	1.05	0.90	0.86
AUC_{0-inf} (μg/mLxh)	100.9±20.25	91.89±21.71	88.29±18.99	1.04	0.91	0.87
C_{max} (μg/mL)	22.10±4.76	13.83±3.234	12.67±3.52	1.09	0.62	0.57
T_{max} (h)	1.552±0.87	3.815±1.521	3.657±1.09	1.04	2.46	2.36
Half life (h)	6.396±1.34	6.158±1.915	6.573±1.74	1.08	1.08	1.00
Rate constant (h)	0.112±0.02	0.121±0.031	0.112±0.03	0.94	0.96	1.03

Table 6

Etodolac Plasma Concentrations in the Food Study (N=18)
Pharmacokinetic Parameters: Least Squares Means ± Standard Error

Parameter	Test-Fast A	Test-Fed B	Ref-Fed C	B/C	B/A	C/A
AUC_{0-t} (μg/mLxh)	96.080±1.46	86.638±1.46	82.847±1.46	1.05	0.90	0.86
AUC_{0-inf} (μg/mLxh)	100.92±1.53	91.894±1.53	88.287±1.53	1.04	0.91	0.87
C_{max} (μg/mL)	22.100±0.81	13.833±0.81	12.672±0.81	1.09	0.62	0.57
T_{max} (h)	1.552±0.243	3.815±0.243	3.657±0.243	1.04	2.46	2.36
$LNAUC_{0-t}$	4.546±0.017	4.439±0.017	4.398±0.017	1.01	0.98	0.97
$LNAUC_{0-inf}$	4.596±0.017	4.497±0.017	4.460±0.017	1.01	0.98	0.97
LNC_{max}	3.074±0.053	2.598±0.053	2.500±0.053	1.04	0.84	0.81

Table 7

Comparative Quantitative Composition of Etodolac 200 mg and 300 mg Capsules

Ingredient	200 mg Capsule mg	200 mg Capsule % of active	300 mg Capsule mg	300 mg Capsule % of active
Intragranular:				
Etodolac, Micronized	200.00	--	300.00	--
Sodium Lauryl Sulfate, NF				
Microcrystalline Cellulose, NF				
Lactose, NF				
Sodium Starch Glycolate, NF				
Povidone, USP				
Sodium Starch Glycolate, NF				
Magnesium Stearate, NF				
Microcrystalline Cellulose, NF				
Total fill weight	468.00		468.00	

Table 8. In Vitro Dissolution Testing

Drug (Generic Name): Etodolac Capsules
Dose Strength: 200 mg, 300 mg
ANDA No.: 74-842
Firm: Endo Laboratories
Submission Date: January 31, 1996
File Name: 74842SDW.196

I. Conditions for Dissolution Testing:

USP XXII Basket:X Paddle: RPM:100
No. Units Tested: 12
Medium: 0.05M Phosphate buffer, pH 7.5 Volume: 1000 mL
Specifications: NLT (Q) released in 30 minutes
Reference Drug: Lodine® Capsules (Wyeth-Ayerst)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # JH233 Strength(mg) 200			Reference Product Lot #3950227 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
5	60.3		7.7	29.3		22.8
10	90.2		4.2	83.0		6.9
20	98.7		2.1	101.8		1.3
30	99.8		2.2	102.4		1.2
45	100.3		2.2	102.9		1.1

Sampling Times (Minutes)	Test Product Lot # JH234 Strength(mg) 300			Reference Product Lot # 3950231 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
5	9.3		39.6	22.4		26.0
10	38.6		28.8	72.0		8.6
20	91.2		4.8	99.7		1.5
30	95.6		1.2	100.2		1.4
45	96.5		0.9	100.5		1.4

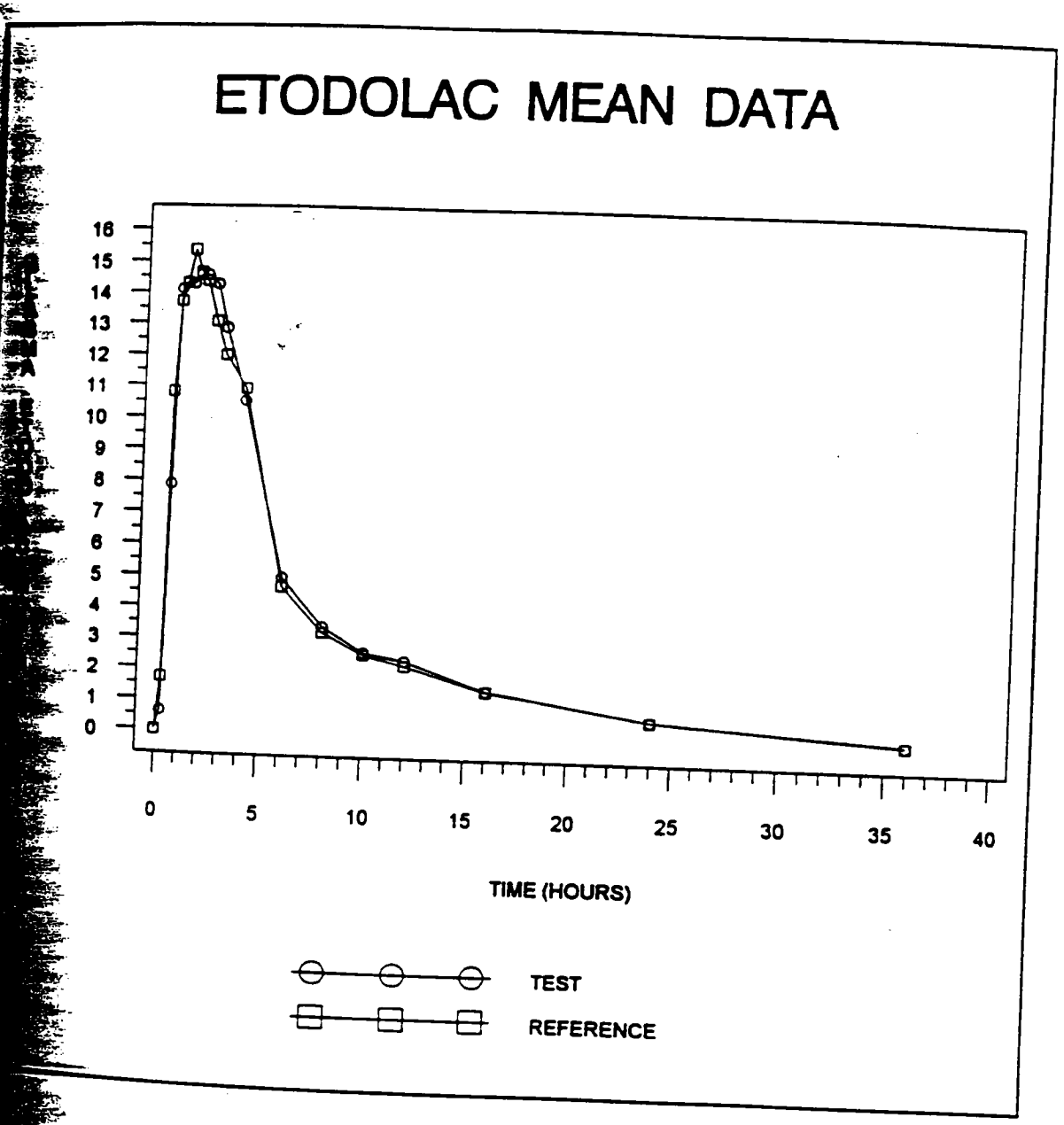

ETODOLAC MEAN DATA
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0
5
10
15
20
25
30
35
40
TIME (HOURS)
TEST
REFERENCE

Figure 1

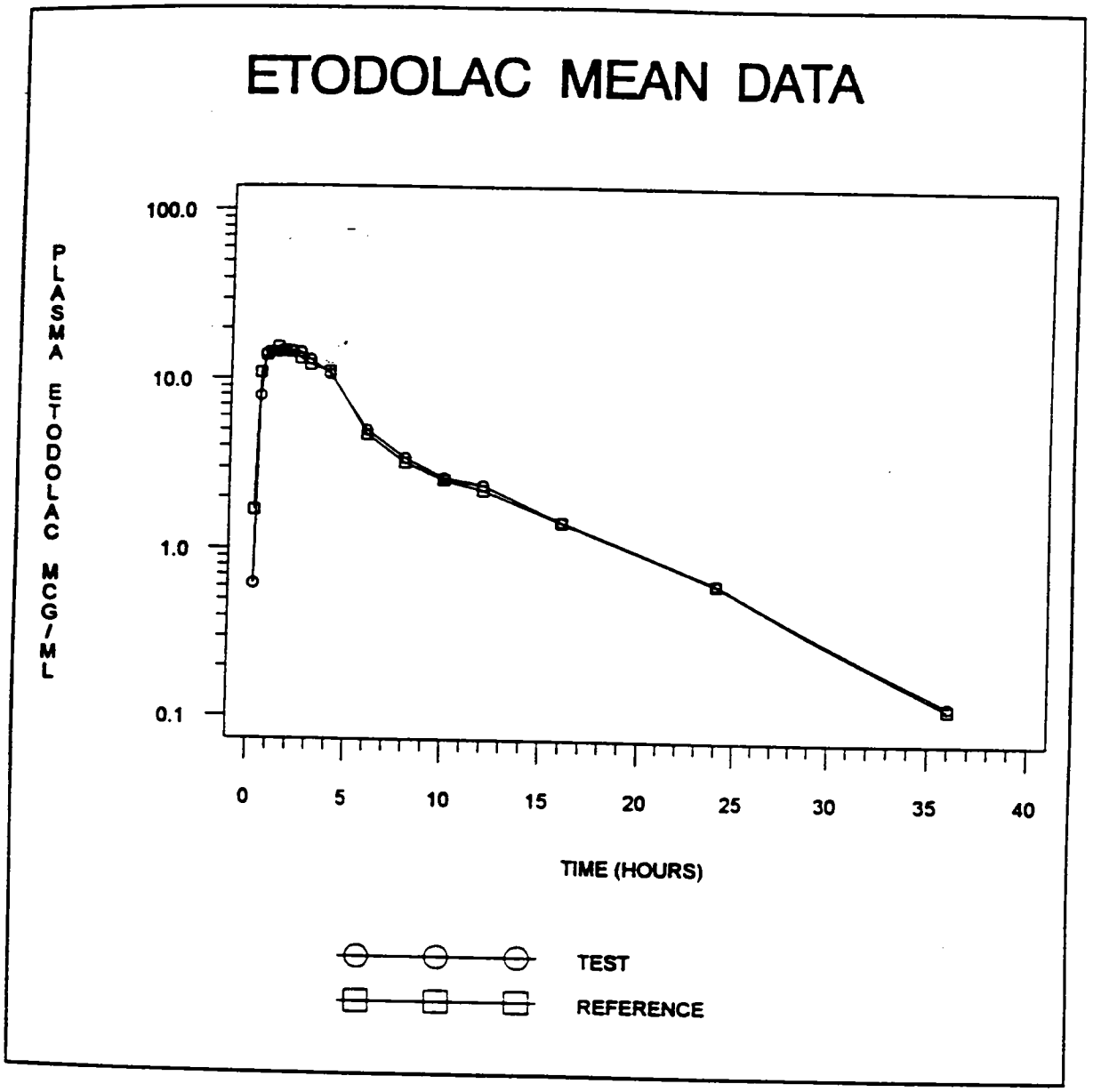

ETODOLAC MEAN DATA
PLASMA ETODOLAC MCG/ML
100.0
10.0
1.0
0.1
0
5
10
15
20
25
30
35
40
TIME (HOURS)
TEST
REFERENCE

Figure 2

Figure 4.5.1 Linear Plot of Mean Plasma Etodolac Concentrations *vs* Time

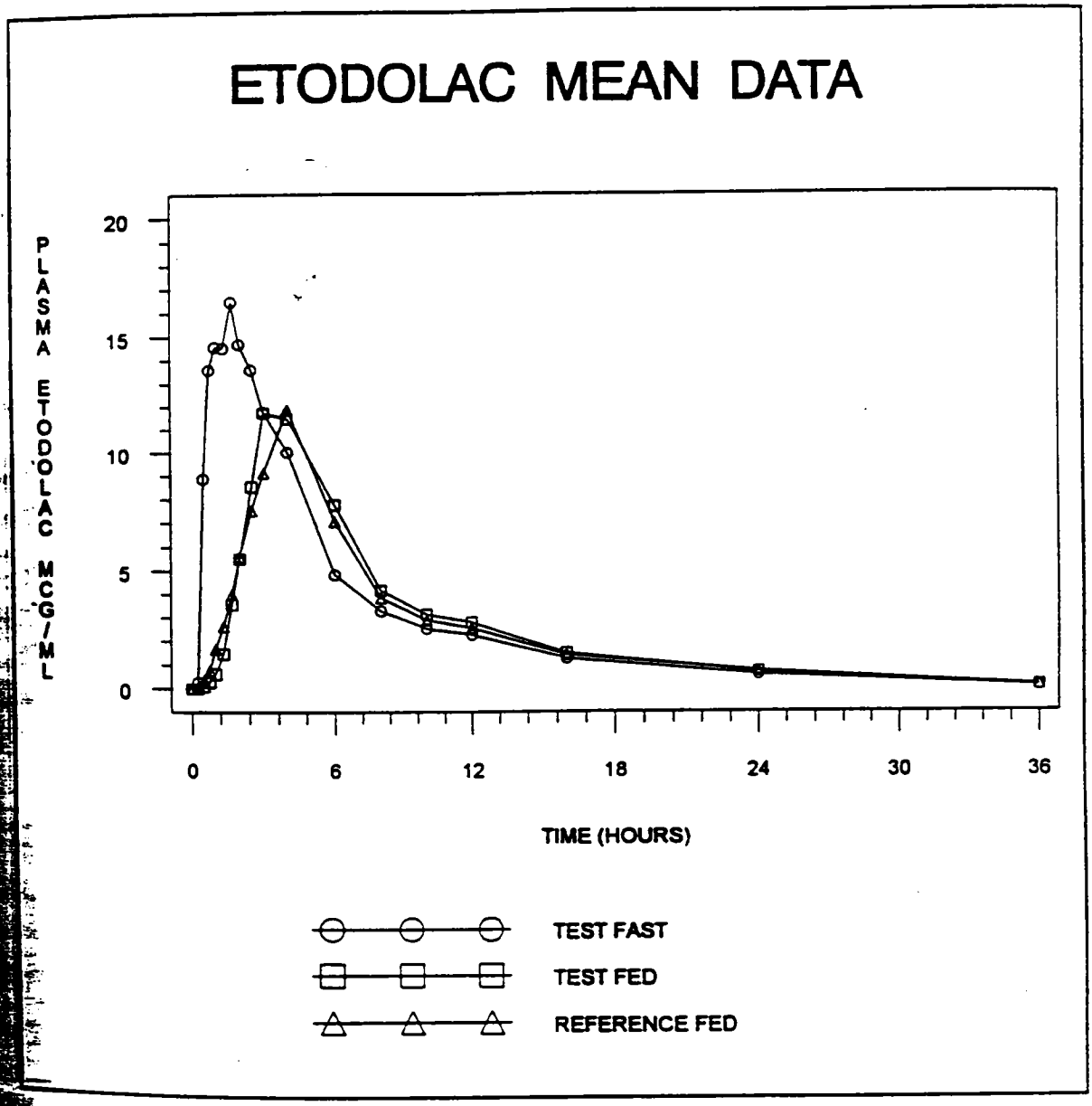


Figure 3

Figure 4.5.2 Semi-logarithmic Plot of Mean Plasma Etodolac Concentrations *vs* Time

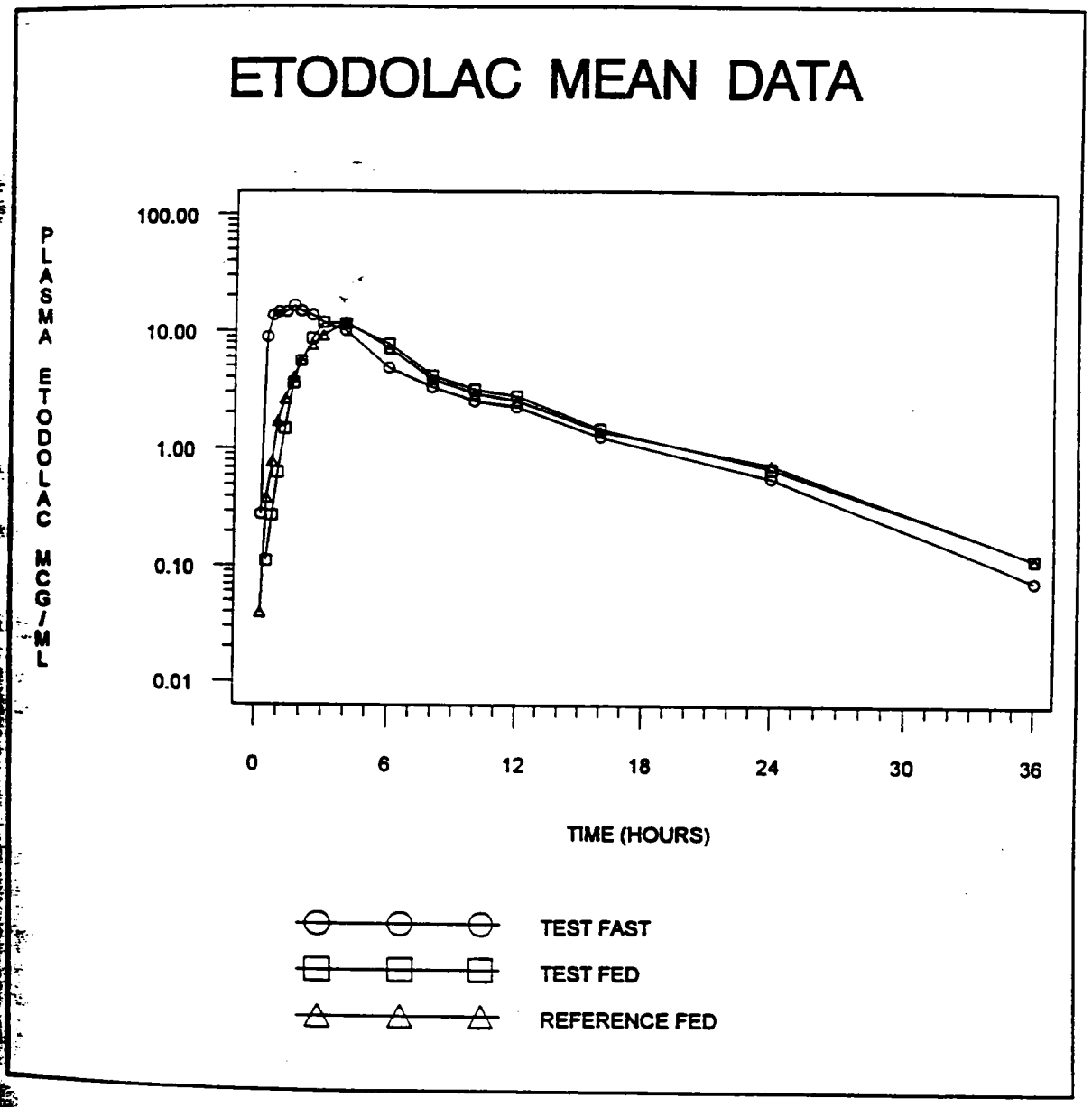


figure 4